

AMENDMENTS TO THE SPECIFICATION

Please amend paragraph 16, beginning on page 6 as follows:

[0016] **Figure 1** shows that intratumoral (i.t.) injection of Ad.PTH.IL-18 inhibited the growth of MCA205 tumors in wild type (WT) mice, but not in *gld* mice, and in turn enhanced CTL activity. Figure 1(A and B) shows the anti-tumor effects of Ad.PTH.IL-18 injection alone, and the limited effectiveness of repeated delivery of IL18 adenoviral vector. WT mice and *gld* mice (five mice per group) received 1×10^5 of MCA205 cells i.d. inoculation in the right flank on day 0. The animals were treated by i.t. injection of HBSS, Ad.EGFP, or Ad.PTH.IL-18 on day 7 and day 10. Data represent the mean \pm S.D. of tumor area. The i.t. injection of Ad.PTH.IL-18 was associated with a significant anti-tumor effect in WT animals ($p=0.003$; WT/Ad.PTH.IL-18 vs. WT/Ad.EGFP, $p=0.003$; WT/Ad.PTH.IL-18 vs WT/HBSS) (A), but not in *gld* mice ($p>0.05$; *gld*/Ad.PTH.IL-18 vs *gld*/Ad.EGFP or *gld*/HBSS) (B). **, $p<0.01$, n.s.; not significant (C) CTL activities after treatment; Data represent the mean \pm S.D. of cytotoxic activity in the duplicate culture cells from regional lymph nodes cells obtained from two mice in each group. On day 7 and day 10 Ad.PTH.IL-18, Ad.EGFP or HBSS was administered, two in each group were sacrificed for the *in vitro* assay on day 14. After 5 days co-cultured with irradiated MCA205 cells, cytotoxic activity was assessed against MCA205 cells (A) and YAC-1 cells (B). There is a statistically significant difference between WT/Ad.PTH.IL-18 vs WT/Ad.EGFP ($p=0.013$) and WT/Ad.PTH.IL-18 vs *gld*/Ad.PTH.IL-18 ($p=0.021$). n.s., not significant. Figure 1C shows the FasL dependent induction of cytotoxicity.

Please amend paragraph 17, beginning on page 6 as follows:

[0017] **Figure 2** shows that coinjection of Ad.PTH.IL-18 and DC induced potent anti-tumor effect against not only injected MCA205 tumor but also non-injected tumor at the distant site. Figure 2A shows that DC combination with adenoviral delivery of IL18 mediates profound antitumor activity in MCA205. Figure 2B shows that interleukin 18 mediates distant antitumor effects when coupled with DC. Figure 2C shows development of systemic immunity with IL18 and dendritic cell coadministration. On day 0, mice

received 1×10^5 MCA205 cells on both the right and left flanks. On day 7 and 10, mice received 1×10^6 DC and 3×10^8 plaque forming units (p.f.u.) of adenoviral vector, or HBSS. Data represent the mean \pm S.D. of tumor area of (A) injected and (B) non-injected tumor area of the animals. (C) Data represent the mean \pm S.D. of cytolytic activity of the cells cultured from regional lymph nodes or spleen harvested from treated animals. On day 7 and day 10, Ad.PTH-IL-18, Ad.EGFP or HBSS and DC were administered; two in each group were sacrificed for the *in vitro* assay on day 14. After 5 days of co-culture with irradiated MCA205 cells, cytotoxic activity was assessed against MCA205 cells and YAC-1 cells.

Please amend paragraph 18, beginning on page 7 as follows:

[0018] **Figure 3** shows that CTL induced by i.t. coinjection of Ad.PTH-IL-18 and DC are tumor specific and MHC class I restricted. ~~In~~ Figure 3(A)[[,]] shows the fine specificity of the antitumor cytolytic response mediated by IL18 and DCs. ~~Cytolytic~~
In Figure 3(A), cytolytic activity was assessed against MCA205 cells, MC38 cells, EL-4 cells, B16 cells, and YAC-1 cells at various effector: target (E:T) ratios. Data represent the mean \pm S.D. of cytotoxicity. There is a significant difference between cytolytic activity against MCA205 cells and those against other targets ($p < 0.01$ for all). ~~In~~ Figure 3(B)[[,]] shows that cytolytic activity mediated by DC and IL18 injection is MHC Class I [K^b] restricted. ~~Effector~~
In Figure 3(B), effector cells were treated with anti-H2K^b antibody, anti-H2K^d antibody, or no antibody at various E:T ratios. Data represent the mean \pm S.D. of cytotoxicity. There was a statistically significant difference between cytotoxicity of the anti-H2K^b treated group and that of the non-treated or anti-H2K^d treated group (*: $p < 0.05$).

Please amend paragraph 19, beginning on page 7 as follows:

[0019] **Figure 4** shows that DCs require IL12 production to mediate antitumor effects with IL18 and shows the involvement of endogenous IL-12 in the anti-tumor effects mediated by AD.PTH-IL-18 and DCs using DCs cultured from IL-12 gene deficient (IL-12 GKO) mice. Coinjection of Ad.PTH-IL-18 and DC from IL-12 GKO mice was

associated with significantly less anti-tumor effects when compared with that of the treatment with DCs from immunocompetent animals.

AMENDMENTS TO THE DRAWINGS

Below is a discussion of the amendments to the drawings.

Figures 1A and 1B, on replacement sheet 1, have been amended to remove the heading “Limited Effectiveness of Repeated Delivery of IL18 Adenoviral Vector”. The letter “A” above the y-axis in Figure 1A has been removed. The letter “B” above the y-axis in Figure 1B has been removed.

Figure 1C, on replacement sheet 2, has been amended to remove the heading “FasL Dependent Induction of Cytotoxicity”.

Figure 2A, on replacement sheet 3, has been amended to remove the heading “DC Combination with Adenoviral Delivery of IL18 Mediates Profound Antitumor Activity in MCA 205”.

Figure 2B, on replacement sheet 4, has been amended to remove the heading “Interleukin 18 Mediates Distant Antitumor Effects When Coupled with DC”.

Figure 2C, on replacement sheet 5, has been amended to remove the heading “Development of Systemic Immunity with IL18 and Dendritic Cell Coadministration”.

Figure 3A, on replacement sheet 6, has been amended to remove the heading “Fine Specificity of the Antitumor Cytolytic Response Mediated by IL18 and DCs”.

Figure 3B, on replacement sheet 7, has been amended to remove the heading “Cytolytic Activity Mediated by DC and IL18 Injection is MHC Class I [K^b] Restricted”.

Figure 4, on replacement sheet 8, has been amended to remove the heading “DCs Require IL12 Production to Mediate Antitumor Effects with IL18”.

Figures 1-4, on replacement sheets 1 through 8, have all been amended to present the figures in black with a white background, as opposed to white with a black background as in the originally filed informal drawings.